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Report

Perirhinal Cortex Supports Encoding and Familiarity-Based Recognition of Novel Associations

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SUMMARY

Results from imaging and lesion studies of item recognition memory have suggested that the hippocampus supports memory for the arbitrary associations that form the basis of episodic recollection, whereas the perirhinal cortex (PRc) supports familiarity for individual items. This view has been challenged, however, by findings showing that PRc may contribute to associative recognition, a task thought to measure relational or recollective memory. Here, using functional magnetic resonance imaging, we demonstrate that PRc activity is increased when pairs of items are processed as a single configuration or unit and that this activity predicts subsequent familiarity-based associative memory. These results explain the discrepancy in the literature by showing that novel associations can be encoded in a unitized manner, thereby allowing PRc to support associative recognition based on familiarity.

INTRODUCTION

The ability to remember past events depends critically on the formation of novel, arbitrary associations. Converging evidence suggests that this ability depends on the integrity of structures in the medial temporal lobes (MTL), and specifically the hippocampus. For instance, according to one view (Aggleton and Brown, 1999; Cohen and Eichenbaum, 1993; Davachi, 2006; Eichenbaum et al., 2007), the hippocampus may rapidly encode novel representations of arbitrary relationships in a manner that can support later recollection. In contrast, it has been suggested that the perirhinal cortex (PRc), a region in the anterior parahippocampal gyrus, encodes representations of specific items in a manner that can support familiarity or item memory strength (Aggleton and Brown, 1999; Norman and O'Reilly, 2003; Yonelinas et al., 2005). Consistent with such models, imaging studies of item recognition have shown that PRc activation is preferentially correlated with item familiarity, whereas hippocampal activity is preferentially correlated with contextual recollection (Diana et al., 2007).

A number of findings, however, potentially challenge this view by suggesting that the PRc may additionally be able to support memory for novel associations. For example, rats (Bunsey and Eichenbaum, 1993) and monkeys (Murray et al., 1993) with hippocampal lesions can show intact learning of novel associations between items, but these forms of associative learning are significantly impaired by PRc lesions. Although human amnesic patients with MTL damage typically show severe impairments in associative recognition, there have been some reports of spared associative recognition in patients with damage restricted to the hippocampus (Mayes et al., 2004; Vargha-Khadem et al., 1997). Single-unit recording studies of monkeys have shown that activity in PRc neurons is strongly correlated with learning and recall of associations between visual objects (Miyashita and Chang, 1988; Naya et al., 2001; Sakai and Miyashita, 1991). Based on the assumption that associative learning is a pure measure of relational or recollective memory, these findings have been interpreted as strong evidence against the idea that the PRc encodes item representations (Squire et al., 2004).

An alternative explanation of the available evidence is that the PRc can support familiarity-based recognition of novel associations if the paired items are encoded as a single unit (Graf and Schacter, 1989) or configuration (Cohen and Eichenbaum, 1993). More specifically, PRc may form representations of pairings if they are treated as components of a coherent single item. During recognition, the familiarity strength of that configuration will be greater than if the pair was not studied together, thereby allowing familiarity to be useful in supporting associative memory discriminations. Consistent with this "unitization hypothesis," behavioral studies have indicated that encoding that promotes unitization of item pairs increases the familiarity of these novel associations (Quamme et al., 2007; Yonelinas et al., 1999), and amnesic patients with hippocampal damage are able to learn associations between pairs of words as long as they are encoded as single compound words (Giovanello et al., 2006; Quamme et al., 2007). These results suggest that regions outside the hippocampus can support familiarity-based associative recognition through unitization (Quamme et al., 2007), but it is not known whether unitization relies on the PRc.

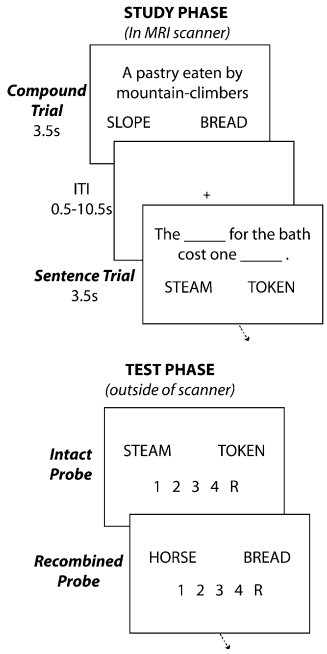

Figure 1. Stimuli and Timing of Events

Participants were scanned during encoding of word pairs. During compound encoding trials, participants were instructed to silently combine pairs of nouns into a novel compound word and rate how well the accompanying definition described the new item. During sentence encoding trials, participants were instructed to mentally insert the nouns into the blanks and rate how well they fit in the sentence. During the test phase, participants made recognition confidence judgments on intact and rearranged versions of word pairs that were previously studied in the scanner.

Here, we used event-related functional magnetic resonance imaging (fMRI) to test the hypothesis that PRc is capable of encoding unitized associations and that it can support accurate familiarity-based recognition of novel associations. Participants were scanned while encoding novel pairs of unrelated nouns (e.g., "STEAM TOKEN," "LIVER TREE") in the context of two different encoding tasks that manipulated the degree to which each pair would be unitized (Figure 1). In the "compound" task, each noun pair was presented along with a definition, and participants rated how well the definition fit this new compound word. In the "sentence" task, each pair was presented with a sentence frame, and participants rated how well the nouns completed the sentence. Thus, during compound trials, participants processed the word pair as a single unit by treating it as a compound word, whereas during the sentence trials they processed the two words within a sentence that preserved the meanings of the separate words. After scanning, participants were given an associative recognition test in which they were to discriminate between intact and rearranged word pairs (e.g., "STEAM TREE") using a memory confidence scale (e.g., Ranganath et al., 2003; Yonelinas et al., 2005).

Although participants encoded pairs of nouns in both conditions, we hypothesized that, during compound trials, participants would additionally process the pair as a novel unitized item. Thus, we predicted that the development of novel item representations during compound trials would elicit increased activation in PRc, as compared with sentence trials. In addition, it was predicted that the strength of these item representations would determine subsequent familiarity for the pairings. Thus, we predicted that PRc activation in this region during encoding should be correlated with subsequent familiarity strength for each pairing.

RESULTS

Behavioral Results

Recognition performance was assessed by plotting receiver operating characteristics (ROCs) for each participant (Macmillan and Creelman, 2005; Swets, 1964). Inspection of these data indicated that associative memory strength was higher for pairs encoded in the compound condition, as compared with pairs from the sentence condition (see Figure 2A). A formal ROC analysis using a dual process model (Yonelinas, 1994) indicated that familiarity estimates were significantly higher in the compound than in the sentence encoding condition [$t(13) = 4.955$, $p < 0.0005$], whereas recollection estimates did not significantly differ [$t(13) < 1$]. Qualitatively similar results were obtained when an unequal variance signal detection model was applied to the data (Swets, 1964): unitization led to an increase in memory strength [$d' = 1.23$ versus 1.58, $t(13) = 2.46$, $p < 0.029$] but did not affect the variance ratio [Vo = 1.48, 1.55, $t(13) < 1$].

fMRI Results

The first contrast tested the prediction that activation in the PRc should be increased during compound encoding trials, compared with sentence encoding trials. As shown in Figure 3A, results were consistent with this prediction. This contrast revealed significant activation in a region of the left anterior parahippocampal gyrus [local maximum at $x = -30$, $y = -15$, $z = -42$ mm; $t(13) = 4.948$] that is most likely within the PRc (Insausti et al., 1998). No suprathreshold voxels were observed in the hippocampus or parahippocampal cortex. The results from the corresponding whole-brain analysis are presented in the Supplemental Data section available online.

The second contrast examined whether activation in the PRc during encoding was predictive of subsequent familiarity-based associative recognition. In this analysis, we used a novel subject-specific analysis method to estimate the mean level of subjective familiarity associated with each confidence bin (see Experimental Procedures for details). This approach was used for two reasons. First, the relationship between familiarity strength and recognition confidence may be nonlinear, and many recognition models assume that familiarity strength has a normal (Gaussian) distribution (Norman and O'Reilly, 2003; Wixted, 2007; Yonelinas, 1994). A second reason is that different participants have a different subjective criterion for each confidence level. In other words, "4" judgments from a participant with a relatively liberal criterion may be associated with much less familiarity than "4" judgments from a participant with a more stringent criterion. To address these issues, single-subject ROC data were used to create parametric covariates that modeled activation during encoding of each pair as a linear function of subsequent familiarity strength (rather than confidence). This "subsequent familiarity" covariate therefore allowed us to identify regions in

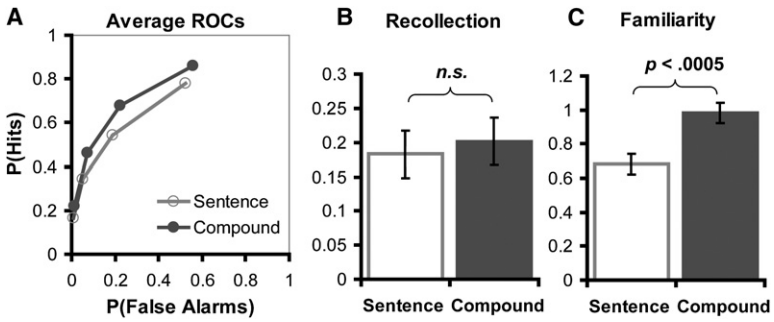

Figure 2. Behavioral Results

Unitization increases familiarity-based recognition of word pairs.

(A) Average ROCs for associative recognition of pairs encoded under compound (filled circles) and sentence (open circles) conditions. Each ROC depicts the cumulative hit (y axis) and false alarm (x axis) rates as the response criterion is varied.

(B and C) Mean estimates of the contribution of (B) recollection and (C) familiarity are plotted. Error bars depict the standard error of the compound-sentence difference. The results show that familiarity was higher for pairs that were encoded on compound trials compared with pairs encoded on sentence trials.

which activation during encoding was linearly correlated with subsequent familiarity for the association.

Results from the analysis revealed significant activation in the left PRc [local maximum at x = −33, y = −12, z = −33 mm; $t(13) = 4.039$]. As shown in Figure 3B, activation in this region increased monotonically with subsequent recognition confidence but did not significantly differ between associations that were confidently recognized on the basis of familiarity and associations that were subsequently recollected [$t(13) = 0.158$, $p = 0.88$]. As with the unitization contrast, no suprathreshold voxels were observed in the hippocampus or parahippocampal cortex. The results from the corresponding whole-brain analysis are presented as Supplemental Data.

The unitization hypothesis predicts that processing a word pair as a single compound word will result in the formation of a new item representation (see Supplemental Data section for results from a separate behavioral experiment that are consistent with this prediction) and that the strength of these item representations supports familiarity. Therefore, we would expect overlap between the MTL regions showing increased activation on compound trials and the regions that were predictive of subsequent familiarity. As shown in Figure 3C, the intersection of the encoding condition and subsequent familiarity contrasts revealed a single cluster of suprathreshold voxels within the MTL in the left PRc. Thus, consistent with the unitization hypothesis, the same region in left PRc exhibited neural correlates of unitization and familiarity. No other clusters in the MTL were observed. The corresponding whole-brain intersection map is illustrated in Figure S1.

DISCUSSION

Several models of the functional organization of the MTL propose that the PRc specifically encodes representations that support familiarity or item memory, whereas the hippocampus encodes representations that support recollection or relational memory (Aggleton and Brown, 1999; Davachi, 2006; Eichenbaum and Cohen, 2001; Eichenbaum et al., 2007). However, some findings suggest that PRc may also support associative recognition, and this evidence has been interpreted as a refutation of models that assume that the PRc encodes item representations (e.g., Squire et al., 2007). In the present study, we tested an alternative view—that the PRc may be able to encode pairings as novel items or configurations and thereby support associative recognition based on familiarity.

Behavioral results revealed that encoding of word pairs as a single, novel compound word selectively increased the contribution of familiarity to associative recognition performance, while having no significant effect on recollection. FMRI results showed that activation in a region of left PRc was increased when participants were encouraged to encode word pairs as a compound word, as compared to when they encoded the pairs in the context of a sentence. Using individual recognition memory ROCs to generate subject-specific familiarity covariates, we found that activation in an overlapping region was predictive of subsequent familiarity on the associative recognition test. Finally, in a separate behavioral study described in the Supplemental Data, we demonstrated that reversing the order of word pairs at test selectively reduced recognition of pairs that were encoded on compound trials, supporting the idea that participants encoded these pairs as novel compound words. Collectively, the results suggest that the PRc can encode novel associations in a unitized or configural manner in a single trial and that the PRc can support associative recognition based on familiarity.

Our findings are consistent with single-unit recording studies showing the existence of object-selective "pair coding" neurons in the PRc that preferentially responded to fractals that had previously been paired together (Sakai and Miyashita, 1991). These pair coding neurons might reflect configural or unitized representations of the fractal pairings that developed over the course of training. Results from our study might also explain previous reports of spared associative recognition following hippocampal damage. That is, whereas recollection may typically support associative memory, animals with hippocampal damage may be forced to rely on PRc representations that can support associative recognition based on familiarity. Consistent with this hypothesis, Sauvage et al. (2008) have shown that rats with hippocampal lesions can learn associations between odors and a digging media (e.g., wood chips, beads, sand). However, analyses of recognition ROCs showed that associative recognition in rats with hippocampal lesions was supported primarily by familiarity, whereas recognition in control rats was supported primarily by recollection. It is unclear whether spared associative recognition in human amnesic patients with hippocampal lesions can be completely explained by unitization or whether there may be other mitigating factors as well (e.g., Mayes et al., 2007). Nonetheless, the present results suggest that future neuropsychological investigations of associative recognition in animals or human amnesics should explicitly test the role of unitization

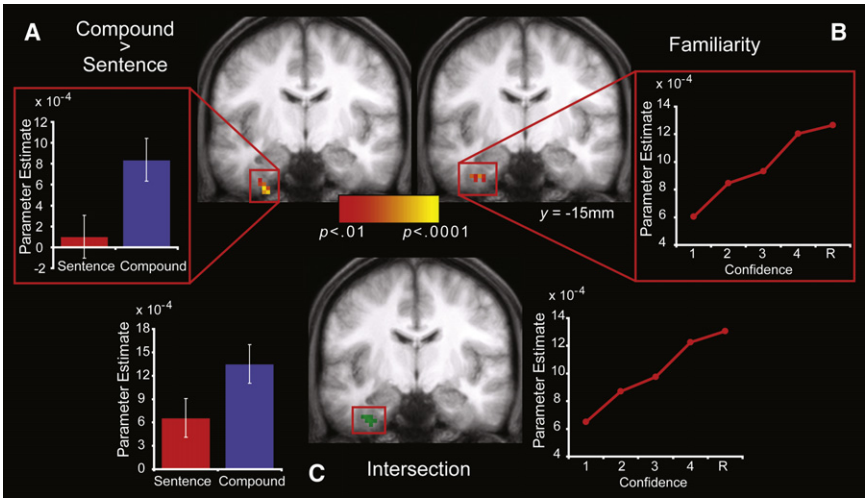

Figure 3. Activation in Left Perirhinal Cortex Is Increased during Unitization of Word Pairs and Correlated with Subsequent Familiarity

(A) MTL voxels in which activation was significantly greater for the compound encoding condition than sentence encoding condition.

(B) MTL voxels in which activation significantly correlated with subsequent familiarity.

(C) Intersection of previous two contrasts revealed a region in left collateral sulcus.

Error bars depict the standard error of the difference. All MRI sections are 15 mm posterior to the anterior commissure. Note: The graphs in panels (B) and (C) depict mean signal change associated with each subsequent confidence bin, but the activation maps in these panels are based on analyses of participant-specific parametric familiarity contrasts (see Experimental Procedures).

as a mechanism that can support associative recognition (see also Giovanello et al., 2006; Quamme et al., 2007).

The present results may also shed light on reports of new semantic learning in amnesic patients with hippocampal damage (Duff et al., 2006; Vargha-Khadem et al., 1997; Verfaellie et al., 2000) by suggesting that the PRc might support new semantic learning. That is, in the compound condition of our experiment, each pair of items was associated with a novel concept that allowed processing of the pair as a novel unitized compound word. It is unlikely that these new concepts were equivalent to concepts that a subject might have learned over a lifetime. Nonetheless, like existing compound words, unitized pairs were extremely sensitive to the specific word order (see Supplemental Data). These results suggest the possibility that the PRc may be able to support acquisition of novel semantic knowledge, even when the hippocampus is damaged.

The idea that the PRc can support memory for unitized associations may explain why PRc activity is rarely associated with recollection in fMRI studies of item recognition, but that it is sometimes correlated with successful associative recognition (Diana et al., 2007). It is possible that, in studies of associative recognition, participants might spontaneously encode associations in a configural or unitized manner, such that item representations in the PRc could support accurate performance based on familiarity. A similar account has been proposed to explain PRc involvement in source recognition. For instance, in two studies, Staresina and Davachi (2006, 2008) demonstrated that PRc activity was correlated with source memory for the background color that was paired with a studied word. Because color information was encoded as an item feature in their experiments, the authors suggested that, under these conditions, item representations formed in PRc could support successful source recognition. Consistent with this idea, Staresina and Davachi (2008) found that PRc activity was not correlated with source memory for contextual information (i.e., the task that was performed). Building on these findings, Diana et al. (2008) showed that the contribution of familiarity to source recognition was increased if participants encoded color information as an item feature, as compared to when they encoded color as an associated contextual detail. Collectively, these findings suggest that the PRc may encode item representations that can support source recognition or associative recognition on the basis of familiarity. Accordingly, researchers should be careful to avoid interpreting performance on associative or source memory tasks as process-pure measures of recollection (Parks and Yonelinas, 2007).

Although the current results did not support the idea that the PRc supports recollection of associations (i.e., no significant differences were observed between recollected and confidently recognized pairs), they also do not rule out the possibility. Indeed, according to the "Binding of Items and Contexts" (BIC) model (Diana et al., 2007), PRc activity during retrieval can be correlated with recollection in response to a partial cue. More specifically, presentation of a familiar context or item cue may elicit activation of the relevant hippocampal relational memory representation ("pattern completion"), thereby resulting in the activation of an associated item representation in PRc. Because we scanned participants during encoding, we could not observe such a recall effect in this study. However, this idea is consistent with reports of object-selective "pair recall" neurons in the PRc, which show increased activity when the associate of the preferred object is presented as a cue (Sakai and Miyashita, 1991), and with unpublished data from our laboratory showing that PRc activity was increased when participants recalled faces in response to a scene context cue (D.E. Hannula and C.R., unpublished data).

The present study did not reveal evidence of a relationship between hippocampal activity and recollection, as is often found in tests of item recognition (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007). This may be attributable to the fact that, in associative recognition, participants may recollect information about individual items even when they fail to recollect the associations between items (i.e., "noncriterial recollection"). Thus, on some trials, participants could have failed to encode the relationship between the two words but still successfully encode contextual information about at least one of the items in the pair. To the extent that this occurred, it would have reduced our ability to detect activation related to recollection (in the hippocampus or elsewhere).

Outside of the MTL, activation in the left inferior frontal gyrus (IFG) was also increased during compound trials, relative to sentence trials. Results from several previous studies suggest that regions in the left IFG may be involved in controlled retrieval or selection of specific stimulus dimensions during item encoding (Badre and Wagner, 2007; Blumenfeld and Ranganath, 2007; Gold and Buckner, 2002; Kan and Thompson-Schill, 2004). It is likely that the IFG activation observed here was driven by similar demands imposed by the compound word task. That is, in order to encode two words as a new compound word, participants may attend to a subset of associations from each of the constituent words, while inhibiting associations irrelevant to the new concept. Interestingly, activation in the same region of the IFG was also predictive of subsequent familiarity. Previous imaging studies have also shown that activation in this region was associated with familiarity-based *item* recognition (Montaldi et al., 2006; Ranganath et al., 2003). These findings add to accumulating evidence (Duarte et al., 2005; MacPherson et al., 2008) against the idea that the prefrontal cortex selectively contributes to recollection.

In conclusion, a number of models have proposed that the PRc encodes representations that support assessments of item familiarity strength (Aggleton and Brown, 1999; Davachi, 2006; Diana et al., 2008; Eichenbaum et al., 2007). Findings from previous studies linking PRc to associative memory have been taken as evidence against these models. The present results may help to reconcile the discrepancy by demonstrating that the PRc can encode configural, unitized representations of novel associations and that these representations can support associative recognition based on familiarity.

EXPERIMENTAL PROCEDURES

Participants

Participants were 16 native English-speaking, right-handed students (seven female), aged 18–35, at the University of California at Davis. Data from two participants (one female) were excluded from analyses because of severe image artifacts due to excessive head movement. All procedures were approved by the University of California, Davis Institutional Review Board.

Stimuli and Design

Stimuli were 576 four- to six-letter English nouns with moderate to high word frequency (10–1000 occurrences per million; Kucera and Francis, 1967), combined to form 288 novel noun pairs. For each noun pair, a corresponding sentence frame was constructed, which had two blanks into which the two nouns could be inserted, and which preserved the separate meanings of the nouns. This sentence frame constituted the prompt for the "sentence" encoding trials. Also for each noun pair, a corresponding definition was created that described the novel item that would result from combining the two nouns into a single compound noun. This definition constituted the prompt for the "compound" encoding trials. Trial sequences and timings were optimized for fMRI using the *optseq* algorithm (Dale, 1999). Intertrial interval was varied from 0.5 to 10.5 s.

The postscan test consisted of 280 intact pairs presented during the study phase, along with recombined versions of these pairs, constructed by repairing the first word in a given pair with the second word from a different pair that was studied in the same encoding condition.

See Supplemental Data for more details on counterbalancing and test design.

Procedure

After informed consent was obtained, participants were instructed for the study phase and completed a short practice run. They were told that they would be reading sentences and definitions and evaluating how well noun pairs fit each of these conditions. The study phase was conducted in the scanner, and stimuli were projected onto a screen at the foot of the scanner bed and viewed via a mirror affixed to the head coil. On "sentence" trials, participants viewed a sentence with two blanks along with a pair of nouns, and they were instructed to use a scale from "1" (very poor fit) to "4" (very good fit) to rate how well the words fit in the context of the sentence. On "compound" trials, participants viewed a definition along with a pair of nouns and were instructed to rate on a 1–4 scale how well the definition described this new word. Each noun pair was presented in only one encoding condition per participant, but was presented equally often in both encoding conditions across participants. (See Figure 1 for samples of experimental stimuli.) During each trial, stimuli were presented for 3.5 s, followed by a jittered intertrial interval (ranging from 0.5 to 10.5 s). During the scanning session, the participant completed seven experimental runs, each consisting of a pseudorandom sequence of 20 compound and 20 sentence trials.

After the study phase was complete, participants were given a surprise test for the word pairs that were seen in the scanner. They were instructed that they would see intact and recombined word pairs presented on the computer screen. For each pair, they were instructed to respond "R" if they could recollect qualitative details about having seen it during the study phase (Yonelinas et al., 2005); otherwise, they were to rate their confidence as to whether the pair was presented at study, from "1" ("very confident *not* studied together") to "4" ("very confident studied together").

Behavioral Data Analysis

During the test phase, confidence ratings were obtained for intact and recombined pairs of words that had been studied in the compound and sentence trials. These data were used to construct separate receiver operating characteristics for the compound and sentence conditions. To quantify the contributions of recollection and familiarity to associative recognition in the two encoding conditions, a dual-process model (Yonelinas, 1994) was fit to each participant's ROCs. In order to test whether the results obtained from this analysis were specific to this model, hits and false alarms were also modeled using an unequal variance signal detection model (Swets, 1964). See Supplemental Data for details on modeling and analysis of ROC data.

fMRI Data Acquisition and Analysis

MRI data was acquired at the UC Davis Imaging Research Center using a 3T Siemens Trio scanner. Functional images were obtained using a gradient echoplanar (EPI) sequence with the following parameters: TR, 2000 ms; TE, 25 ms; FOV, 220 mm; matrix size, 64 × 64. Each functional volume consisted of 34 3.4 mm axial slices with no interslice gap, resulting in a voxel size of 3.4375 × 3.4375 × 3.4 mm. High-resolution, T1-weighted coplanar images and 3D volumes were also acquired from each participant. An additional set of functional images was acquired while participants performed a visual-motor response task, in order to estimate subject-specific hemodynamic response functions (HRFs) (Handwerker et al., 2004).

Prior to analysis, the EPI data were sinc interpolated to correct for timing differences in acquisition of adjacent slices, realigned using a six-parameter, rigid-body transformation, spatially normalized to the Montreal Neurological Institute (MNI) EPI template, resliced into 3 mm isotropic voxels, and spatially smoothed with an isotropic 6 mm Gaussian filter.

Changes in the blood oxygen level-dependent (BOLD) fMRI signal associated with encoding task and with subsequent familiarity were estimated using a modified general linear model (Worsley and Friston, 1995), as implemented in the Voxbo software suite (http://www.voxbo.org). Two orthogonal binomial covariates were constructed to model changes in activity during compound and sentence trials.

An additional parametric covariate was constructed to indicate the level of familiarity of each trial stimulus in the subsequent associative recognition test. Using individual-participant recognition responses, covariates were constructed for each encoding condition that indexed changes in neural activity that increased linearly with subsequent familiarity strength. Trials with "R" ratings were excluded so that the covariate could specifically model activity that was predictive of subsequent familiarity. For each remaining

confidence level k, the following equation was used to estimate mean familiarity strength f_k:

$$\hat{f}_k = Z\left(C_k - \frac{P_k}{2}\right)$$

where C_k is the cumulative proportion of responses with ratings less than or equal to k, P_k is the proportion of responses with ratings equal to k, and $Z(x)$ is the inverse normal cumulative distribution function (that is, the function that, given a probability, outputs a z score).

A "subsequent familiarity" covariate was created by replacing the confidence rating for each stimulus with the estimated familiarity score for that confidence level. These parametric covariates were then mean-centered. MATLAB code for computing these covariates is available from the authors on request.

All covariates were independently convolved with a subject-specific HRF that was empirically derived for each participant based on BOLD responses in the central sulcus during a motor response task (Handwerker et al., 2004). Additional covariates of no interest were constructed to model motion-correlated signal changes, spikes in the time series, non-task-correlated global signal changes, shifts in the signal baseline between experimental runs, and an intercept. Frequencies above 0.25 Hz and below 0.005 Hz were removed from the time series, and a linear regression was performed to identify voxel-wise correlations between the three covariates of interest and the BOLD signal. This analysis yielded a set of parameter estimates for each covariate.

For the group analysis of activity differences between the sentence and compound conditions, a contrast image comparing parameter estimates from the two conditions was prepared for each participant. These contrast images were entered into a second-level, one-sample t test in which the group mean difference value for each voxel was tested against zero. A similar approach was used in the group analyses of subsequent familiarity covariates. It was expected that participants likely engaged in some degree of unitization during both types of trials (Quamme et al., 2007), though this should occur to a much greater extent on compound trials. Accordingly, these covariates were summed across encoding conditions in order to maximize the ability to detect changes in activation predictive of subsequent familiarity. Images of these collapsed contrasts for each subject were entered into a t test. MTL regions showing suprathreshold activation were identified using a voxel-wise threshold of $p < 0.01$ and a cluster size threshold to correct for multiple comparisons within the MTL. The size of the cluster threshold was determined by creating an region of interest mask that included bilateral hippocampus, entorhinal cortex, PRc, and parahippocampal cortex, based on criteria established by Insausti et al. (1998). Using the AlphaSim program in the AFNI software package (http://afni.nimh.nih.gov/afni/), a Monte Carlo analysis was performed on this volume, and a minimum cluster size threshold of 11 voxels was determined to ensure a family-wise error rate of $p < 0.05$. The mask was applied to the uncorrected activation map, and activations surviving the cluster threshold were identified.

A separate analysis was conducted in order to visualize the degree of PRc activation associated with each confidence rating. In this analysis, a separate covariate was used to model responses associated with each subsequent confidence rating (i.e., 1, 2, 3, 4, or R). The model was prepared and analyzed using the same procedure described above. Parameter estimates for each confidence bin were averaged across voxels within the PRc ROIs, and across-subject mean values were plotted in Figures 3B and 3C).

In order to identify MTL regions that showed effects of both encoding condition and familiarity, we generated uncorrected activation maps for each contrast as above using a threshold of $p < \sqrt{.0005}$. The resulting activation maps were corrected for multiple comparisons as described above. Because of the more liberal voxel-wise threshold, a larger cluster threshold (18 voxels) was used to constrain the family-wise error rate at $p < 0.05$ (however this adjustment did not eliminate any additional clusters in the MTL, compared with an 11 voxel threshold). Voxels with suprathreshold values in both maps were then identified in the intersection map. For archival purposes, fMRI results for regions outside the MTL region of interest are described in the Supplemental Data section.

SUPPLEMENTAL DATA

The Supplemental Data can be found with this article online at http://www.neuron.org/cgi/content/full/59/4/554/DC1/.

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REFERENCES

Aggleton, J.P., and Brown, M.W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav. Brain Sci. *22*, 425–444.

Badre, D., and Wagner, A.D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia *45*, 2883–2901.

Blumenfeld, R.S., and Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist *13*, 280–291.

Bunsey, M., and Eichenbaum, H. (1993). Critical role of the parahippocampal region for paired-associate learning in rats. Behav. Neurosci. *107*, 740–747.

Cohen, N.J., and Eichenbaum, H. (1993). Memory, Amnesia, and the Hippocampal System (Cambridge, MA: MIT Press).

Dale, A.M. (1999). Optimal experimental design for event-related fMRI. Hum. Brain Mapp. *8*, 109–114.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. Curr. Opin. Neurobiol. *16*, 693–700.

Diana, R.A., Yonelinas, A.P., and Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. Trends Cogn. Sci. *11*, 379–386.

Diana, R.A., Yonelinas, A.P., and Ranganath, C. (2008). The effects of unitization on familiarity-based source memory: Testing a behavioral prediction derived from neuroimaging data. J. Exp. Psychol. Learn. Mem. Cogn. *34*, 730–740.

Duarte, A., Ranganath, C., and Knight, R.K. (2005). Effects of unilateral prefrontal lesions on familiarity, recollection, and source memory. J. Neurosci. *25*, 8333–8337.

Duff, M.C., Hengst, J., Tranel, D., and Cohen, N.J. (2006). Development of shared information in communication despite hippocampal amnesia. Nat. Neurosci. *9*, 140–146.

Eichenbaum, H., and Cohen, N.J. (2001). From Conditioning to Conscious Recollection: Memory Systems of the Brain (New York: Oxford University Press).

Eichenbaum, H., Yonelinas, A.R., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. Annu. Rev. Neurosci. *30*, 123–152.

Giovanello, K.S., Keane, M.M., and Verfaellie, M. (2006). The contribution of familiarity to associative memory in amnesia. Neuropsychologia *44*, 1859–1865.

Gold, B., and Buckner, R. (2002). Common prefrontal regions coactivate with dissociable posterior regions during controlled semantic and phonological tasks. Neuron *35*, 803–812.

Graf, P., and Schacter, D.L. (1989). Unitization and grouping mediate dissociations in memory for new associations. J. Exp. Psychol. Learn. Mem. Cogn. *15*, 930–940.

Handwerker, D.A., Ollinger, J.M., and D'Esposito, M. (2004). Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. Neuroimage *21*, 1639–1651.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P., and Pitkänen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am. J. Neuroradiol. *19*, 659–671.

Kan, I.P., and Thompson-Schill, S.L. (2004). Selection from perceptual and conceptual representations. Cogn. Affect. Behav. Neurosci. *4*, 466–482.

Kucera, H., and Francis, W.N. (1967). Frequency Analysis of English Usage: Lexicon and Grammar (Boston: Houghton Mifflin).

Macmillan, N.A., and Creelman, C.D. (2005). Detection Theory: A User's Guide, Second Edition (New York: Cambridge University Press).

MacPherson, S.E., Bozzali, M., Cipolotti, L., Dolan, R.J., Rees, J.H., and Shallice, T. (2008). Effect of frontal lobe lesions on the recollection and familiarity components of recognition memory. Neuropsychologia, in press. Published online July 12, 2008. 10.1016/j.neuropsychologia.2008.07.003.

Mayes, A.R., Holdstock, J.S., Isaac, C.L., Montaldi, D., Grigor, J., Gummer, A., Cariga, P., Downes, J.J., Tsivilis, D., Gaffan, D., et al. (2004). Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. Hippocampus *14*, 763–784.

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. Trends Cogn. Sci. *11*, 126–135.

Miyashita, Y., and Chang, H.S. (1988). Neuronal correlate of pictorial short-term memory in the primate temporal cortex. Nature *331*, 68–70.

Montaldi, D., Spencer, T.J., Roberts, N., and Mayes, A.R. (2006). The neural system that mediates familiarity memory. Hippocampus *16*, 504–520.

Murray, E.A., Gaffan, D., and Mishkin, M. (1993). Neural substrates of visual stimulus-stimulus association in rhesus monkeys. J. Neurosci. *13*, 4549–4561.

Naya, Y., Yoshida, M., and Miyashita, Y. (2001). Backward spreading of memory-retrieval signal in the primate temporal cortex. Science *291*, 661–664.

Norman, K.A., and O'Reilly, R.C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. Psychol. Rev. *110*, 611–646.

Parks, C.M., and Yonelinas, A.P. (2007). Moving beyond pure signal-detection models: comment on Wixted. Psych. Rev. *114*, 188–202.

Quamme, J.R., Yonelinas, A.P., and Norman, K.A. (2007). Effect of unitization on associative recognition in amnesia. Hippocampus *17*, 192–200.

Ranganath, C., Yonelinas, A.P., Cohen, M.X., Dy, C.J., Tom, S.M., and D'Esposito, M. (2003). Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia *42*, 2–13.

Sakai, K., and Miyashita, Y. (1991). Neural organization for the long-term memory of paired associates. Nature *354*, 152–155.

Sauvage, M.M., Fortin, N.J., Owens, C.B., Yonelinas, A.P., and Eichenbaum, H.J. (2008). Recognition memory: Opposite effects of hippocampal damage on recollection and familiarity. Nat. Neurosci. *11*, 16–18.

Squire, L.R., Stark, C.E., and Clark, R.E. (2004). The medial temporal lobe. Annu. Rev. Neurosci. *27*, 279–306.

Squire, L.R., Wixted, J.T., and Clark, R.E. (2007). Recognition memory and the medial temporal lobe: a new perspective. Nat. Rev. Neurosci. *8*, 872–883.

Staresina, B.P., and Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. J. Neurosci. *26*, 9162–9172.

Staresina, B.P., and Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. J. Cogn. Neurosci. *20*, 1478–1489.

Swets, J.A. (1964). Signal Detection and Recognition by Human Observers: Contemporary Readings (New York: Wiley).

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. Science *277*, 376–380.

Verfaellie, M., Koseff, P., and Alexander, M.P. (2000). Acquisition of novel semantic information in amnesia: effects of lesion location. Neuropsychologia *38*, 484–492.

Wixted, J.T. (2007). Dual-process theory and signal-detection theory of recognition memory. Psychol. Rev. *114*, 152–176.

Worsley, K.J., and Friston, K.J. (1995). Analysis of fMRI time-series revisited - again. Neuroimage *2*, 173–182.

Yonelinas, A.P. (1994). Receiver-operating characteristics in recognition memory: evidence for a dual-process model. J. Exp. Psychol. Learn. Mem. Cogn. *20*, 1341–1354.

Yonelinas, A.P., Kroll, N.E., Dobbins, I.G., and Soltani, M. (1999). Recognition memory for faces: when familiarity supports associative recognition judgments. Psychon. Bull. Rev. *6*, 654–661.

Yonelinas, A.P., Otten, L.J., Shaw, K.N., and Rugg, M.D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. J. Neurosci. *25*, 3002–3008.